

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Attorney Docket No. 017227/0176**

In re patent application of

Barry L. REED *et al.*

Filed: July 24, 2001

Group Art Unit: Unassigned

Serial No.: Unassigned

Examiner: Unassigned

Divisional of Serial No. 09/125,436, filed December 18, 1998

For: DERMAL PENETRATION ENHANCERS AND DRUG DELIVERY SYSTEMS INVOLVING SAME

**PRELIMINARY AMENDMENT**

Commissioner of Patents  
Washington, D.C. 20231

Sir:

We are simultaneously filing herewith a divisional application of United States Serial No. 09/125,436, filed December 18, 1998. Please enter the following amendment in the divisional application.

**IN THE SPECIFICATION:**

On page 1, on the line below the title, insert - - This is a divisional application of U.S. Serial No. 09/125,436, filed December 18, 1998, which is a national phase of PCT/AU97/00091 filed February 19, 1997 - -.

**IN THE CLAIMS:**

Please cancel claims 1-38 and add the following new claims:

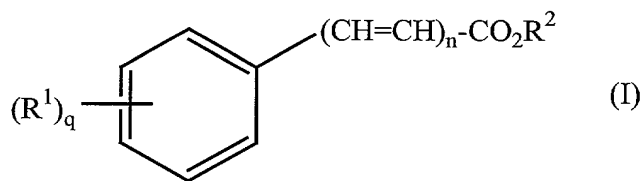
39. A transdermal drug delivery system which comprises:

a therapeutically effective amount of at least one physiologically active agent or prodrug thereof; and

at least one dermal penetration enhancer present in an amount of from 10 to 10,000 wt% based on the weight of the active agent or prodrug thereof; wherein the dermal penetration enhancer is at least one of

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a safe skin-tolerant ester sunscreen of formula (I):



wherein R<sup>1</sup> is hydrogen, lower alkyl, lower alkoxy, halide, hydroxy or NR<sup>3</sup>R<sup>4</sup>;

R<sup>2</sup> is a C<sub>6</sub> to C<sub>18</sub> alkyl,

R<sup>3</sup> and R<sup>4</sup> are each independently hydrogen, lower alkyl or R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;

n is 0 or 1, and

q is 1 or 2,

wherein when n is 0 and R<sup>1</sup> is NR<sup>3</sup>R<sup>4</sup>, then NR<sup>3</sup>R<sup>4</sup> is para-substituted.

40. A drug delivery system according to claim 39, wherein said ester is a C<sub>8</sub> to C<sub>18</sub> alkyl para-aminobenzoate, C<sub>8</sub> to C<sub>18</sub> alkyl dimethyl-para-aminobenzoate, C<sub>8</sub> to C<sub>18</sub> alkyl cinnamate, C<sub>8</sub> to C<sub>18</sub> alkyl methoxycinnamate or C<sub>8</sub> to C<sub>18</sub> alkyl salicylate

41. A drug delivery system according to claim 40, wherein said ester is octyl dimethyl-para-aminobenzoate, octyl para-methoxycinnamate or octyl salicylate.

42. A drug delivery system according to claim 39, further comprising a pharmaceutical compounding agent, co-solvent, surfactant, emulsifier, antioxidant, preservative, stabiliser, diluent or a mixture of two or more of said components.

43. A transdermal drug delivery system as claimed in claim 39, further comprising at least one volatile liquid.

44. A non-occlusive, percutaneous or transdermal drug delivery system which comprises:

(i) a therapeutically effective amount of at least one physiologically active agent or prodrug thereof;

(ii) at least one dermal penetration enhancer, which is present in an amount of from 10 to 10,000 wt% based on the weight of the active agent or prodrug thereof;

(iii) at least one volatile liquid present in an amount to act as a vehicle for the active agent and penetration enhancer;

wherein:

the dermal penetration enhancer (A) is adapted to transport the physiologically active agent across a dermal surface or mucosal membrane of an animal, when the volatile liquid evaporates, to form a reservoir or depot of a mixture comprising the penetration enhancer and the physiologically active agent within said surface or membrane, and (B) is of low toxicity to, and is tolerated by, the dermal surface or mucosal membrane of the animal; and,

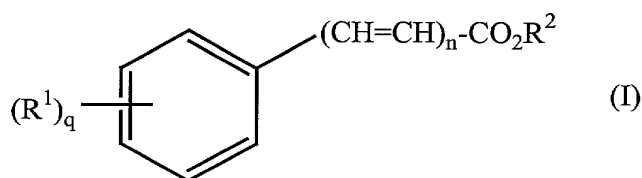
after application of the system to an area of the dermal surface or mucosal membrane, the area becomes touch-dry within 3 minutes of application.

45. A drug delivery system according to claim 44, wherein the drug delivery system is not supersaturated with respect to the physiologically active agent.

46. A drug delivery system according to claim 44, wherein the dermal surface or mucosal membrane becomes touch-dry within 1 minute of application.

47. A drug delivery system according to claim 44, wherein the dermal penetration enhancer is a safe skin tolerant sunscreen.

48. A drug delivery system according to claim 44, wherein said ester is of formula (I):



wherein R<sup>1</sup> is hydrogen, lower alkyl, lower alkoxy, halide, hydroxy or NR<sup>3</sup>R<sup>4</sup>;

R<sup>2</sup> is a long chain alkyl;

R<sup>3</sup> and R<sup>4</sup> are each independently hydrogen, lower alkyl or R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;

n is 0 or 1; and

q is 1 or 2.

49. A drug delivery system according to claim 44, wherein said ester is a long chain alkyl para-aminobenzoate, long chain alkyl dimethyl-para-aminobenzoate, long chain alkyl cinnamate, long chain alkyl methoxycinnamate or long chain alkyl salicylate.

50. A drug delivery system according to claim 49, wherein said ester is octyl dimethyl-para-aminobenzoate, octyl para-methoxycinnamate or octyl salicylate.

51. A drug delivery system according to claim 44, wherein the volatile liquid is ethanol or isopropanol.

52. A drug delivery system according to claim 39 or claim 44, wherein the physiologically active agent is a steroid, hormone derivative, non-steroidal anti-inflammatory drug, opioid analgesic, antinauseant, antioestrogen, aromatase inhibitor, 5-alpha reductase inhibitor, anxiolytic, prostaglandin, anti-viral drug, anti-migraine compound, antihypertensive agent, anti-malarial compound, bronchodilator, anti-depressant, anti-Alzheimer's agent, neuroleptic and antipsychotic agent, anti-Parkinson's agent, anti-androgen or anorectic agent.

53. A drug delivery system according to claim 39 or claim 44, wherein the physiologically active agent is testosterone, oestradiol, ethinyloestradiol, progesterone, norethisterone acetate, ibuprofen, ketoprofen, flurbiprofen, naproxen, diclofenac, fentanyl, buprenorphine, scopolamine, prochlorperazine, metochlopramide, ondansetron, tamoxifen, epitioestanol, exemestane, 4-hydroxy-androstenedione and its derivatives, finasteride, turosteride, LY191704, MK-306, alprazolam, alprostadil, prostacyclin and its derivatives, melatonin, n-docosanol, tromantadine, lipophilic pro-drugs of acyclovir, low molecular weight heparin, enoxaparin, sumatriptan, amlodipine, nitrendipine, primaquine, minoxidil, minoxidil pro-drugs, pilocarpine, salbutamol, terbutaline, salmeterol, ibogaine, bupropion, rolipram, tacrine, fluphenazine, haloperidol, N-0923, cyproterone acetate or mazindol.

54. A drug delivery system according to claim 44, wherein the system is applied to the dermal surface by an aerosol, as a spray.

55. A drug delivery system according to claim 54, wherein the aerosol is a fixed or variable metered dose aerosol.

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56. A drug delivery system according to claim 44, further comprising a pharmaceutical compounding agent, co-solvent, surfactant, emulsifier, antioxidant, preservative, stabiliser, diluent or a mixture of two or more of said components.

57. A method for administering at least one systemic or locally acting physiologically active agent or prodrug thereof to an animal which comprises applying an effective amount of the physiologically active agent in the form of a drug delivery system according to claim 39 or claim 44 to a dermal surface or mucosal membrane of said animal.

58. A method for the treatment or prophylaxis of a disease or condition in an animal which comprises administering to a dermal surface or mucosal membrane of said animal in need of such treatment a therapeutically effective amount of the drug delivery system according to claim 39 or claim 44 to a dermal surface or mucosal membrane of said animal.

59. A method according to claim 58, wherein the disease or condition requires male hormone replacement in testosterone deficient hypogonadal men, female hormone replacement therapy for postmenopausal women, androgen replacement therapy for females lacking libido, male contraception or female contraception.

60. A method according to claim 58, wherein the disease or condition is soft tissue injury, narcotic withdrawal, severe post-operative pain, motion sickness, oestrogen dependent breast cancer, prostatic enlargement and/or prostatic cancer, alopecia and acne, anxiety disorders, male impotence, Raynaud's syndrome and varicose veins, sleep disorders, jetlag, herpes virus infections, deep vein thrombosis, migraine, high blood pressure, malaria, diagnosis of cystic fibrosis, asthma or nocturnal asthma.

61. A method according to claim 57, wherein the animal is a human.

62. A transdermal drug delivery system according to claim 39 that further comprises at least one volatile liquid present in an amount to act as a vehicle for the active agent and penetration enhancer.

63. A transdermal drug delivery system according to claim 44, wherein the physiologically active agent or prodrug thereof, the dermal penetration enhancer, and the volatile liquid are a single phase.

64. A method according to claim 57, wherein the drug delivery system is applied by an aerosol or spray comprising a shroud adapted to keep an actuator nozzle of the apparatus at a pre-determined height above the site of application.

**REMARKS**

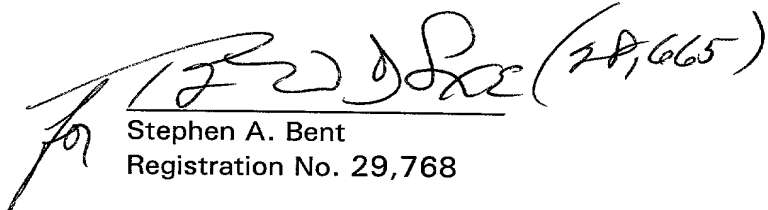
This application is a divisional of U.S. Application Serial No. 09/125,436, filed December 18, 1998. Entry of the above amendments is respectfully requested. New claims 39-64 substantially correspond to originally filed claims 1, 3-5, 10, 12, 15, 16-31 and 39-41, respectively. No new matter has been entered.

If the Examiner has any questions regarding this submission, he is invited to contact the undersigned attorney at the telephone number set forth below.

Respectfully submitted,

July 24, 2001

Date

  
Stephen A. Bent  
Registration No. 29,768

**FOLEY & LARDNER**

Suite 500, 3000 K Street, N.W.  
Washington, D.C. 20007-5109  
(202) 672-5300  
(202) 672-5599

Should additional fees be necessary in connection with the filing of this paper, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees.